Remarks/Arguments begin on page 7 of this paper.

REMARKS

Claims 1-11 are pending in the present application. Claims 10 and 11 were previously withdrawn from consideration as drawn to a non-elected invention. By this amendment, claims 12 and 13 are added. Support for new claims 12 and 13 is found in the specification, *inter alia*, on page 18, paragraph [0057]. Accordingly, claims 1-9, 12, and 13 are currently under consideration. No new matter has been added.

With respect to all claim amendments and cancellations, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Objections to the specification

A. The Examiner objects to the specification, alleging that the title is not indicative of the claimed invention.

In response, Applicants have replaced the title with the one that the Examiner suggested. Accordingly, this objection should be withdrawn.

B. The Examiner also objects to the specification by alleging that it contains embedded hyperlinks and/or other form of browser-executable code.

In response, Applicants have amended the specification to change the embedded hyperlink "http://www.rna-tec.com/repair.htm" on page 35 into "the World Wide Web at rna-tec.com/repair.htm." A similar amendment was made to delete the embedded hyperlinks on page 36. Applicants believe these amendments should address the Examiner's concerns. Applicants have not found any other embedded hyperlinks or browser-executable code in the specification. Applicants respectfully request that this objection be withdrawn.

Claim rejections under 35 U.S.C. §103

A. Claims 1-3 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ro *et al.* (Pain. 79:265-274, 1999; cited by Applicants) in view of Zhorov *et al.* (U.S. Pat. No. 4,389,404). The Examiner states that Ro *et al.* teach that an anti-NGF antibody might be a potential alternative analgesic for pain in humans; and Zhorov *et al.* teach the administration of the opioid analgesic morphine to treat pain. Based on these documents, the Examiner alleges that the claimed invention is obvious over Ro *et al.* in view of Zhorov *et al.* because it would have been obvious to combine these references and one skilled in the art would have been motivated to co-administer morphine and an anti-NGF antibody and would have expected success from this combined treatment.

Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. MPEP §2143.01. Additionally, there must be a reasonable expectation of success. MPEP §2143.02.

Claims 1-3 are directed to a method for treating pain by administering to an individual an effective amount of an anti-NGF antibody and an opioid analgesic, whereby the anti-NGF antibody and the opioid analgesic in conjunction provide effective pain relief.

Applicants submit that neither the cited references nor the general knowledge of one skilled in the art teach or suggest the specific combination of an anti-NGF antibody and an opioid analgesic for the treatment of pain. For example, previous publications in the field indicate that it is not clear to one skilled in the art which analgesics can be combined with another analgesic to achieve additive pain relief. Applicants submit a reference by Sunshine *et al.* Pharmacology 27, Suppl. 1, 31-40, 1983. This paper shows that there was no difference in efficacy in a clinical trial comparing the efficacy of aspirin to the combination of aspirin plus the opioid codeine in pain treatment. *See*, Abstract; Table II; and Figures 1 and 2. Thus, the combination of aspirin and codeine provides no additive effect in pain treatment. In view of this example, one skilled in the art would not

reasonably be motivated to specifically choose the combination of an anti-NGF antibody and an opioid analgesic out of the numerous possible analgesics for the purpose of providing an additive effect in pain relief. On this ground, the obviousness rejection may be properly withdrawn.

Additionally, Applicants respectfully submit that one skilled in the art did not have a reasonable expectation of success, *i.e.*, the expectation that an anti-NGF antibody and an opioid analgesic when used in conjunction would provide enhanced pain treatment or allow a reduced dosage of opioid to effect the same amount of pain reduction.

As taught in Applicants' specification, the claimed invention has significant advantages over the use of an anti-NGF antibody or an opioid alone for treating pain and prior combinations of pain medicines (such as those taught by Sunshine *et al.*) that do not have enhanced efficacy. For example, the Applicants' specification teaches:

> [b]y the use of a nerve growth factor antagonist and an opioid analgesic in conjunction, in accordance with the present invention, it is now possible to treat pain with a lower dose of an opioid analgesic thereby reducing the likelihood of side-effects associated with opioid analgesic usage (e.g. respiratory depression, constipation, renal colic, nausea and vomiting, and tolerance and dependence and the associated problem of drug withdrawal).

Paragraph [0029].

This successful improvement in pain treatment is demonstrated in Example 1 of the present application. Specifically, treatment with the anti-NGF antibody Mab 911 in conjunction with the opioid analgesic morphine was more effective in reducing resting pain than treatment with morphine alone or with antibody alone. *See* paragraphs [0169] to [0177]. For example, Figure 1 shows the resting pain score measured in animals that received 0.3 mg/kg of anti-NGF antibody 911 and 0, 0.3 mg/kg body weight or 1.0 mg/kg body weight of morphine. Data in Figure 1 indicate that treatment with the combination of the anti-NGF antibody and morphine "was more effective in reducing resting pain than morphine alone or anti-NGF antibody alone." Paragraph [0174]. Additionally, Figure 2 shows the resting pain score measured in animals receiving 1.0 mg/kg of

anti-NGF antibody 911, and 0, 0.3 mg/kg body weight, or 1 mg/kg body weight of morphine. Again, "the anti-NGF antibody plus morphine was more effective in reducing resting pain than morphine alone or anti-NGF antibody alone." Paragraph [0175]. Moreover, Figure 3 depicts the resting pain scores after treatment with 0.3 mg/kg or 1 mg/kg of anti-NGF antibody and with 0, 0.3 mg/kg and 1 mg/kg body weight morphine.

Regarding the significant improvement in pain reduction that was achieved from these combinations of anti-NGF antibody and morphine, Applicants' specification teaches:

> Treatment with 0.3 mg/kg of morphine in combination with either 0.3 mg/kg anti-NGF antibody or 1 mg/kg anti-NGF antibody significantly improved pain relief as compared with treatment with 0.3 mg/kg morphine alone. . . . Further, treatment with anti-NGF antibody at 1.0 mg/kg in combination with treatment with morphine at 0.3 mg/kg yielded pain relief at least equal to that obtained with 1 mg/kg of morphine alone. These results demonstrated that treatment with an anti-NGF antibody reduced the amount of morphine needed for effective pain relief.

Paragraph [0176].

These results indicate that the combination treatment is additive in pain reduction. In addition, treatment in conjunction with an anti-NGF antibody reduces the amount of morphine needed for effective pain relief thereby reducing the likelihood of side-effects associated with opioid usage.

Applicants respectfully submit that one skilled in the art would not have had a reasonable expectation that an additive effect in pain reduction could be achieved by administering an anti-NGF antibody in conjunction with an opioid analgesic. None of the references cited by the Examiner teaches or suggests administering anti-NGF antibody in conjunction with an opioid analgesic or the advantage of using this combination treatment. As noted above, previous publications in the field teach away from the claimed combination treatment by indicating that it is not clear to one skilled in the art which analgesics can be combined with another analgesic to

achieve additive pain relief. *See*, Sunshine *et al.* Pharmacology 27, Suppl. 1, 31-40, 1983 (copy enclosed). Given that Sunshine *et al.* demonstrate that the combination of aspirin and codeine provides no additive effect in pain treatment (*see*, Abstract; Table II; and Figures 1 and 2), one skilled in the art would not have reasonably expected that administration of both an anti-NGF antibody and an opioid analgesic would provide an additive effect in pain relief. Based on Sunshine *et al.*, further exploration was necessary to achieve such an improvement in pain relief. On this ground, the obviousness rejection may be properly withdrawn.

In view of the above, the Examiner has not established a *prima facie* case of obviousness.

Applicants further assert that even if a *prima facie* case of obviousness was established, such a rejection can be overcome by showing that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. MPEP §2144.08(II)(B). As noted above, Example 1 in Applicants' specification provides evidence that the combination of the anti-NGF antibody Mab 911 and the opioid morphine provides an unexpected and significant improvement in pain relief.

Accordingly, Applicants respectfully request that this rejection be withdrawn.

B. Claims 1-7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ro *et al.* (Pain. 79:265-274, 1999; cited by Applicants) in view of Zhorov *et al.* (U.S. Pat. No. 4,389,404) as applied to claims 1-3 above, and further in view of Hongo *et al.* (Hybridoma. 19(3):215-27, 2000; cited by Applicants) and Hoogenboom *et al.* (WO 93/06213; cited by Applicants). The Examiner states that Hongo *et al.* teach humanized antibodies that bind with a binding affinity of about 10 nM or less than 10 nM, and Hoogenboom *et al.* teach how to make human antibodies. The Examiner alleges that it was obvious to combine these references, and that there was motivation to do so with a reasonable expectation of success.

Applicants respectfully traverse this rejection.

As discussed above, neither Ro *et al.* nor Zhorov *et al.* teach or suggest that administration of an anti-NGF antibody in conjunction with an opioid analgesic provides additive pain relief; and

one skilled in the art would not have had a reasonable expectation that this additive effect in pain relief could be achieved by the claimed combination treatment. Hongo *et al.* and Hoogenboom *et al.* do not provide any additional suggestions for the combination treatment as claimed. Hongo *et al.* teach a panel of mouse monoclonal antibodies that specifically bind to human NGF. Hoogenboom *et al.* teach how to generate humanized antibodies from a parent antibody. Therefore, one skilled in the art would not have had the required motivation or reasonable expectation of success for the administration of an anti-NGF antibody in conjunction with an opioid analgesic for an additive effect in pain relief.

In view of the above, the Examiner has not established a *prima facie* case of obviousness. As noted above, the unexpected improved ability of the claimed combination treatment methods to enhance pain relief further support the non-obviousness of claims 1-7. Applicants respectfully request that this rejection be withdrawn.

Double Patenting

A. Claims 1-9 stand provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 9-10 of copending Application No. 10/783,730 (U.S. 2004/0253244 A1) in view of the Breault *et al.* (U.S. Pat. No. 5,843,942).

Applicants respectfully request that this rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending App. Ser. No. 10/783,730, at which time Applicants will address this issue.

B. Claims 1-9 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4-7 of copending Application No. 10/682,638 in view of Zhorov *et al.* (U.S. Pat. No. 4,389,404).

Applicants respectfully request that this rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending App. Ser. No. 10/682,638, at which time Applicants will address this issue.

C. Claims 1-4 and 7 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, and 6 of copending Application No. 10/791,162 in view of Zhorov *et al.* (U.S. Pat. No. 4,389,404).

Applicants respectfully request that this rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending App. Ser. No. 10/791,162, at which time Applicants will address this issue.

D. Claims 1-4 and 7 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20, 22, 36, and 37 of copending Application no. 11/104,248 in view of Zhorov *et al.* (U.S. Pat. No. 4,389,404).

Applicants respectfully request that this rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending App. Ser. No. 11/104,248, at which time Applicants will address this issue.

E. Claims 1-4, 6, and 7 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10, and 12-14 of copending Application No. 11/102,201.

Applicants respectfully request that this rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending App. Ser. No. 11/102,201, at which time Applicants will address this issue.

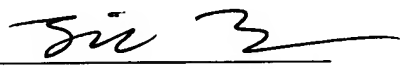
CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 514712000600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: October 16, 2006

Respectfully submitted,

By 

Jie Zhou
Registration No.: 52,395
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-5922

Pharmacology 27: suppl. 1, pp. 31–40.(1983)

0031-7012/83/0277-0031$2.75/0

Oral Analgesic Efficacy of Suprofen Compared to Aspirin, Aspirin plus Codeine, and Placebo in Patients with Postoperative Dental Pain

Abraham Sunshine, Ivan Marrero, Nancy Z. Olson, Eugene M. Laska, Nilda McCormick

New York University Medical Center, New York, N.Y., USA;
University of Puerto Rico School of Dentistry, San Juan, Puerto Rico;
Information Sciences Division, Rockland Research Institute, Orangeburg, N.Y., USA

Key Words. Suprofen · Aspirin plus codeine · Aspirin · Third molar extraction

Abstract. The purpose of this study was to evaluate the analgesic efficacy and safety of single oral doses of suprofen 200 and 400 mg, compared with aspirin 650 plus codeine 60 mg, aspirin 650 mg, and placebo in the relief of moderate to severe pain resulting from the surgical removal of impacted third molars. 157 patients completed a randomized, double-blind, single-dose, stratified, parallel-groups trial, and were observed for at least 4 h. Based upon each of the summary efficacy measures, sum pain intensity difference (SPID), percent SPID, TOTPAR and a global evaluation, all four active treatments were approximately equally effective and all were statistically superior to placebo. In addition, suprofen at both dose levels was significantly more effective than placebo beginning at the 0.5-hour observation for mean pain intensity, whereas the two aspirin treatments were not superior to placebo until the 1-hour observation. Side effects were minimal; there was one in the suprofen 200 mg, three in the aspirin 650 mg, and one in the placebo treatment group. Thus, it appears that suprofen at 200 and 400 mg is a safe and effective oral analgesic for the relief of moderate or severe postoperative dental pain, and it is possible that compared to aspirin 650 mg and aspirin 650 mg plus codeine 60 mg, it has a more rapid onset of action.

Suprofen, α-methyl-4-(2-thienylcarbonyl)-benzene acetic acid, is a new peripherally acting analgesic with anti-inflammatory and antipyretic activity [1]. Activity on prostaglandin biosynthesis from several species and tissues indicates that suprofen is a tissue-selective inhibitor of prostaglandin synthesis [2]. In animal models, suprofen was characterized as having a rapid onset of action with analgesic activity still evident at 4 h after oral

administration [3]. In the rat it is rapidly absorbed, distributed, and eliminated, thus contributing to its rapid onset of action and low risk of drug accumulation [4]. In the adjuvant-induced polyarthritic rat flexion test, suprofen was shown to be 50 times more potent than acetaminophen, 5 times more potent than codeine, and equipotent to zomepirac, diflunisal, and ibuprofen [2, 3]. This pharmacokinetic profile suggests that suprofen may be effectively utilized in the treatment of various painful conditions.

The present clinical trial was undertaken to assess the analgesic efficacy and safety of two dose levels of suprofen, given as single oral doses, compared to aspirin, the combination of aspirin plus codeine, and placebo for the relief of postoperative dental pain.

Subjects and Methods

The study was carried out at the University of Puerto Rico School of Dentistry in San Juan, Puerto Rico and utilized a double-blind, parallel-group, single-dose design. The study population consisted of healthy male or female patients, 18 years of age or older (16 years with parental consent), who had experienced an acute episode of moderate or severe pain after undergoing the surgical removal of one or more third molar impactions under local anesthesia (xylocaine 2% with epinephrine 1/100,000). Pregnant or lactating females and patients with sensitivity to aspirin or codeine-like drugs, a history of significant gastrointestinal, cardiovascular, renal, or hepatic disorders, or known systemic or gastrointestinal bleeding disorders were excluded from the investigation, as were patients with a history of drug dependence. After surgery and after providing written informed consent for study participation, patients remained at the clinic for several hours to be interviewed by the nurse-observer.

Patients were randomly assigned to receive one of five single-dose treatment regimens, suprofen 400 mg, suprofen 200 mg, aspirin 650 mg plus codeine sulfate 60 mg, aspirin 650 mg, or placebo. To maintain double-blind conditions all medications were supplied in identically-appearing capsules, four of which were administered to each patient. Patients were also stratified according to moderate or severe initial pain to ensure balanced treatment groups with respect to initial pain severity. No medications that might confound the interpretation of the efficacy and/or adverse effect liability of the study analgesics were permitted concomitantly or during the 6 h before taking the test medication.

When a patient's postextraction pain was either moderate or severe, double-blind study medication was administered by the nurse-observer. Patients were observed in the clinic for at least 4 and up to 6 h after receiving the study drug. Because it was possible for patients to leave the clinic before completing the 6 h, patients had to have completed a minimum of 4 h to be included in the statistical analysis. The same nurse-observer interviewed the patients at baseline, 0.5, 1, 2, 3 and 4 h (5 and 6 when possible) after study drug administration. At each observation, patients were asked to classify the intensity of their pain as none (0); slight (1); moderate (2); or severe (3), and to indicate whether the relief of pain from the starting pain was none (0); a little (1); some (2); a lot (3); or complete (4). In addition, patients were asked at each observation to indicate any side effects related to the study medication. At the final observation, patients were also requested to evaluate their overall impression of the study medication as excellent (4), very good (3), good (2), fair (1) or poor (0).

Patients were allowed to remedicate with a standard analgesic if insufficient pain relief was obtained with the study medication. The number of patients in each treatment group who were able to complete the evaluation period without receiving additional therapy was regarded as an indication of the analgesic efficacy and duration of action of the test medication. Any patient who remedicated within the first 2 h of the evaluation period was excluded from the analysis of efficacy. For purposes of statistical analysis, patients who required remedication after 2 h and before completion of the evaluation period had their pain intensity and pain relief scores at time of remedication carried through to the end of the evaluation period.

Statistical Methods

The statistical analysis utilized standard methodology for the analysis of such data [5]. Several measurements of analgesia were derived from the inter-

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Results

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view data. Pain intensity difference (PID) is the difference between the pain intensity score at an observation point and the baseline intensity. The sum of the pain intensity differences (SPID) is the sum of the PID scores, weighted by the time interval between observations and is an estimate of the area under the time-effect curve of the treatment. In a 4-hour study the maximum possible SPID is 8 or 12, depending on whether the patient had an initial pain intensity of moderate or severe. Because the initial pain intensities could either be moderate or severe, the variable SPID was normalized as follows: percent SPID (%SPID) is defined for each patient to be the ratio of the patient's SPID score to the maximum possible SPID (depending on the baseline intensity) times 100. The variable TOTPAR (Total in prior publications by these investigators) is the sum of the hourly relief values also weighted by the length of the time interval between observations. Derived pain score onset is defined as the time halfway between the first assessment period at which a change in PID is reported and the previous observation. For purposes of analysis, if patients obtained no relief, their onset was assumed to be 4.5 or 6.5 h based on whether they completed 4 or 6 h of observation, respectively. Time to peak is defined as the time after drug administration that maximum PID occurs. The other parameters are defined analogously. In addition, safety was assessed by evaluation of the type and incidence of any side effects reported.

A comparison was made among the five treatments using a one-way analysis of variance (ANOVA) to test the hypothesis of no difference between treatments for all parameters. When the ANOVA was significant at the $p < 0.05$ level, tests were performed to investigate pairwise differences between treatments using Peritz's modification of the Newman-Keuls procedure [6] and Tukey's A test [7].

Results

Treatments were dispensed to a total of 203 patients, 46 of whom participated in the study twice. The results obtained from the second participation were not used in the efficacy analysis but are included in the safety analysis. In addition, 9 patients, 5 in the placebo group, 2 in the suprofen 200 mg group, and 1 each in the aspirin 650 mg plus codeine 60 mg group and the suprofen 400 mg group, were excluded from the efficacy analysis because of remedication with another analgesic within less than 2 h after taking the study medication (tables I and III). Although not included in the analysis of efficacy, these patients were included in the analysis of safety.

The study was originally designed to include a 6-hour postoperative evaluation period, but only 34 of the 157 patients completed this entire period, primarily because of the requirement to be in attendance at the study site. Thus, the statistical analyses are based on data from 148 patients who completed at least 4 h of observation.

The distribution of some of the characteristics of the study population are shown in table I. There were no significant differences among treatment groups for any of these variables. The initial pain scores were similar and the majority of the patients reported moderate pain. Mean values and an indication of which treatment differences were significant are shown in table II, and time-effect curves for mean pain intensity and pain relief are shown in figures 1 and 2, respectively. Patients in all four active treatment groups reported a marked reduction in pain intensity throughout the 4-hour postoperative evaluation period. Substantial pain reduction began at 0.5 h after initial dosing for the two suprofen groups, and at 1 h for the aspirin plus codeine and aspirin 650 mg groups. Maximum pain reduction was reached on the average of 90 min postdosing for all active treatments with the exception of aspirin 650 mg, which had an average time-to-peak of 100 min postdosing. A similar pattern was observed with pain relief scores (fig. 2).

Table I. Pretreatment patient characteristics

Characteristics	Treatment				
	suprofen 400 mg	suprofen 200 mg	aspirin 650 mg plus codeine 60 mg	aspirin 650 mg	placebo
Total patients enrolled	41	40	41	41	40
Number of dropouts[1]	14	7	9	11	14
Sex (number of patients valid for efficacy)					
Male	10	6	14	7	10
Female	17	27	18	23	16
Mean weight, lb	134.3	125.6	135.8	123.6	132.3
Mean height, in	65.2	63.5	64.9	63.7	64.3
Mean age, years	23.1	23.5	22.7	22.8	22.6
Range, years	18–33	15–47[2]	16–41	16–44	16–29
Baseline pain severity					
Moderate	22	24	26	22	21
Severe	5	9	6	8	5

[1] A total of 55 patients were excluded from the efficacy analysis but were included in the safety data; 46 of these were second entry patients and 9 were remedicated within the first 2 h of the study.
[2] Protocol deviation that was allowed.

Table II. Measures of analgesic efficacy

Variable	Suprofen 200 mg n=33	Suprofen 400 mg n=27	Aspirin 650 mg codeine 60 mg n=32	Aspirin 650 mg n=30	Placebo n=26
Baseline mean pain intensity	2.27	2.19	2.19	2.27	2.19
Pain intensity scores					
0.5 h	1.09*	0.85*	1.19	1.27	1.77
1 h	0.45*	0.33*	0.41*	0.73*	1.46
2 h	0.24*	0.07*	0.38*	0.47*	1.42
3 h	0.39*	0.11*	0.59*	0.43*	1.35
4 h	0.67*	0.44*	0.75	0.37*	1.31
SPID	7.09*	7.52*	6.47*	6.80*	3.65
TOTPAR	12.82*	13.82*	12.08*	12.25*	6.67
Percent SPID	79.23*	85.26*	73.57*	75.28*	39.58
Pain score onset, min	21.82*	27.78*	36.56*	48.50*	109.04
Relief score onset, min	23.64*	27.78*	39.38*	63.50*	125.77
Time to peak, min	72.73*	75.56*	78.75*	100.00*	166.15
Overall impression of study drug	2.75*	3.04*	2.66*	2.67*	1.39

Efficacy analysis is based on 148 patients who were first entry patients and who completed at least 4 h of observation.
* Significantly superior to placebo ($p \leq 0.05$).

Table III. Time to remedi

Treatment	
Suprofen 200 mg	
Suprofen 400 mg	
Aspirin 650 mg plus codeine	
Aspirin 650 mg	
Placebo	

.. Includes all 157 first ent
1 9 Patients remedicated v
2 Total number of remedi

Placebo was clearl
treatment for all param
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placebo were seen fo
scores as well as the
SPID, TOTPAR, % S
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Table III. Time to remedication

Treatment	Time at which remedication occurred						Number[2] of patients
	<2 h[1]	2 h	3 h	4 h	5 h	6 h	
Suprofen 200 mg	2	0	3	2	0	0	7/35
Suprofen 400 mg	1	0	0	1	0	0	2/28
Aspirin 650 mg plus codeine 60 mg	1	1	1	2	1	0	6/33
Aspirin 650 mg	0	1	1	0	0	0	2/30
Placebo	5	8	1	1	0	0	15/31

Includes all 157 first entry patients only; second entry patients are excluded.

[1] 9 Patients remedicated within less than 2 h were excluded from the efficacy analysis.

[2] Total number of remedicated patients/sample size of treatment group for first entry patients.

Placebo was clearly the least effective treatment for all parameters. Significant pairwise differences between each treatment and placebo were seen for most of the hourly scores as well as the summary variables, SPID, TOTPAR, % SPID, pain and relief score onset and time to peak. For the hourly pain intensity scores, suprofen at both dose levels was significantly superior to placebo beginning with the 0.5 h and continuing through to the 4-hour evaluation. Aspirin plus codeine and aspirin alone were statistically superior to placebo beginning at 1 h and continuing through the 3-hour evaluation for the combination and through the 4-hour for aspirin alone. No significant pairwise differences were seen among any of the active treatment groups for the hourly or summary variables. Patients' rating of the overall effectiveness of the medication revealed that placebo was considered to be the least effective treatment, while suprofen 400 mg was rated as the most effective. All active treatments were statistically more effective than placebo for the patients' overall impression of study drug but no significant differences were seen among the active treatment groups.

Remedication

The study was designed to encourage patients to wait at least 2 h before requesting remedication with another analgesic. 9 patients required remedication within less than 2 h and were therefore excluded from the efficacy analysis. 23 of the 148 patients reported in the efficacy evaluation, obtained inadequate pain relief and requested remedication after 2 h. The greater number of patients who required remedication were in the placebo group followed by the aspirin plus codeine combination, suprofen 200 mg and aspirin 650 mg groups; the least number of patients were seen in the suprofen 400 mg group (table III).

Safety and Tolerability

At the time of each evaluation, patients were given an opportunity to report any side effects which they had noted since the previous evaluation. In addition, side effects noted by the study-observer were also recorded.

5 patients reported adverse reaction, 1 in the suprofen 200 mg group, 3 in the aspirin 650 mg group, and 1 in the placebo group (ta-

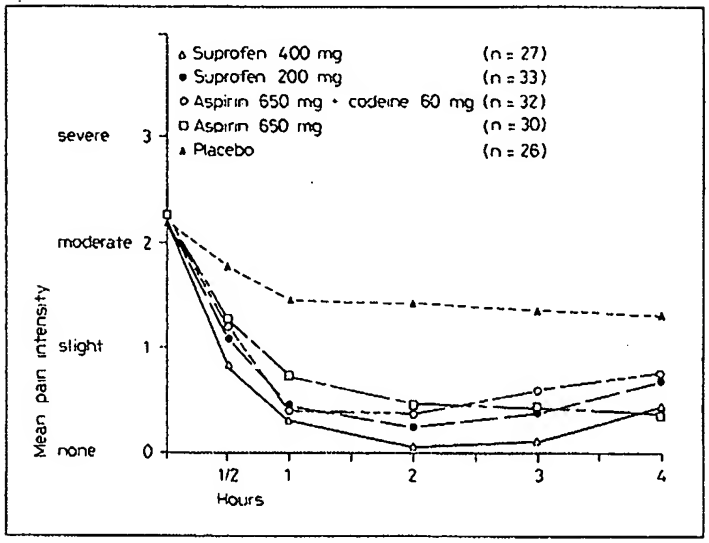

Fig. 1. Time effect curve: mean pain intensity for 4-hour data. Patient responses for pain intensity were scored as 0 = none, 1 = slight, 2 = moderate, and 3 = severe pain. n = Number of subjects.

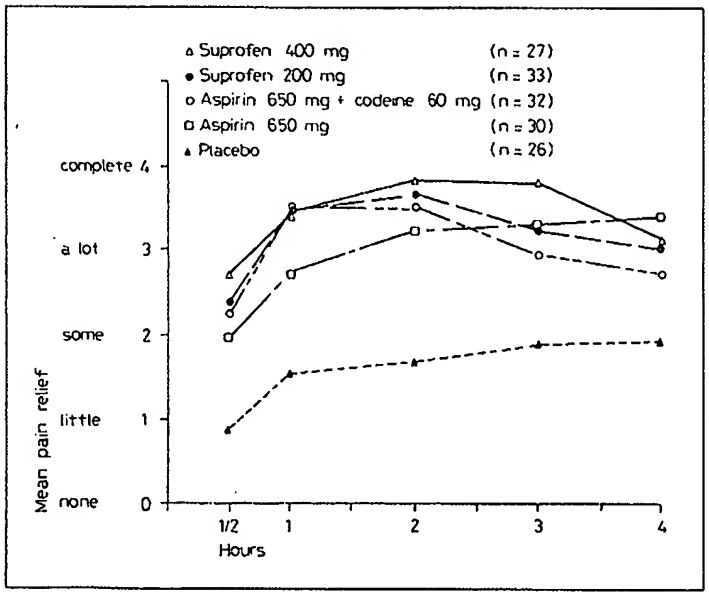

Fig. 2. Time effect curve: mean pain relief for 4-hour data. Mean pain relief is plotted as the degree of the initial pain that was relieved. Patient responses were scored using a five-point scale: 0 = no relief, 1 = a little, 2 = some, 3 = a lot, and 4 = complete relief. n = Number of subjects.

ble IV). The most commonly reported side effect was sleepiness, which was reported by 3 patients. Moderate sleepiness was reported by 1 patient in the suprofen 200 mg group and 1 patient in the aspirin 650 mg group; mild sleepiness was reported by 1 patient in the aspirin 650 mg group. Other side effects reported were severe nausea (1 patient in the aspirin 650 mg group) and vomiting (1 patient in the placebo group).

Table IV. Incidence of side ef

Side effect	
Number of patients reporting side effects	
Sleepiness	
Nausea	
Vomiting	

Numbers in parentheses ref reported on all patients (n = 20

Discussion

Not infrequently a parti to differentiate graded dc or the added effect of a ce such as codeine, to an drug. There are many po for this including the spe of the test drugs, the sp and clinical characteristi the magnitude of the p variability associated wit tions. Commonly an inte graded doses of a standa trial as a measure of the nate. Unfortunately, this clude this feature. This st a significant dose resp Moreover, the addition did not improve the a aspirin. Recently, *Kaik* that the narcotic drugs, s are less effective in a you an older one. The avera

Table IV. Incidence of side effects

Side effect	Suprofen 400 mg n=40 (4)	Suprofen 200 mg n=41 (2)	Aspirin 650 mg plus codeine 60 mg n=41 (1)	Aspirin 650 mg n=41 (1)	Placebo n = 40 (0)
Number of patients reporting side effects	0	1	0	3	1
Sleepiness	0	1	0	3	0
Nausea	0	0	0	1	0
Vomiting	0	0	0	0	1

Numbers in parentheses refer to patients entering the same treatment group more than once. Safety is reported on all patients (n = 203) enrolled in the study, including first and second entry participation.

Discussion

Not infrequently a particular study will fail to differentiate graded doses of active drug or the added effect of a centrally acting drug, such as codeine, to an anti-inflammatory drug. There are many possible explanations for this including the specific pharmacology of the test drugs, the specific demographic and clinical characteristics of the patients, the magnitude of the pain, and the large variability associated with subjective evaluations. Commonly an internal control such as graded doses of a standard are included in a trial as a measure of the ability to discriminate. Unfortunately, this design does not include this feature. This study did not produce a significant dose response for suprofen. Moreover, the addition of codeine to aspirin did not improve the analgesic response to aspirin. Recently, *Kaiko* et al. [8] reported that the narcotic drugs, specifically morphine, are less effective in a younger population than an older one. The average age of our population was 23 years. If the hypothesis of *Kaiko* et al. [8] is correct and can be applied to oral codeine, this would help explain the latter results. An alternative possibility is that the etiology of the pain in this study population is inflammatory and therefore codeine may be less effective. Further studies are necessary to clarify which factors may influence the response to codeine.

Nonetheless, this study demonstrates the usefulness of a new peripherally acting analgesic, suprofen, for the relief of postoperative dental pain. Suprofen 200 and 400 mg was statistically superior to placebo and approximately equally effective to aspirin 650 mg alone and in combination with 60 mg of codeine with respect to all efficacy and safety parameters evaluated. The mean time for pain score onset was about 20 min faster for suprofen at both dose levels than for aspirin 650 mg, and time to peak was approximately 30 min faster with suprofen than with aspirin 650 mg. While these differences were not statistically significant, these data, to-

gether with the mean pain intensity scores at 0.5 h suggest that suprofen is more rapidly acting than aspirin and reaches a peak effect in a shorter period of time.

Suprofen was well tolerated at both dose levels. Only one side effect was reported in 1 patient in the 200 mg group, while 3 patients in the aspirin 650 mg, and 1 in the placebo group reported side effects. These adverse side effects were not considered significant.

Conclusion

Based on this study, suprofen 200 and 400 mg appears to be a safe and effective oral analgesic similar to aspirin and aspirin plus codeine, with the suggestion of a more rapid onset of action. Side effects were minimal.

Die Wirksamkeit oraler Dosen von Suprofen, verglichen mit Aspirin, Aspirin und Codein und Placebos bei der Behandlung von postoperativen Zahnschmerzen

Zusammenfassung. Diese Studie vergleicht die Schmerzlinderung und Sicherheit oraler Einzeldosen von 200 und 400 mg Suprofen mit 650 mg Aspirin und 60 mg Codein, 650 mg Aspirin und Placebos während der Schmerzbehandlung von mittleren bis starken Schmerzen, verursacht durch die chirurgische Entfernung retinierter Weisheitszähne. 157 Patienten nahmen an einer doppelblinden, stratifizierten Parallelgruppen-Studie teil, wobei sie für mindestens vier Stunden nach einer einmaligen Dosis beobachtet wurden. In allen Parametern waren die Wirksubstanzen einander ähnlich und alle waren den Placebos statistisch überlegen. Zusätzlich war Suprofen in beiden Dosierungsmengen nach 30 min bezüglich der durchschnittlichen Schmerzintensität bedeutend wirksamer als Placebo. Die Behandlung mit den beiden Aspirinmengen war in keiner Weise besser für die ersten 60 min. Nebenwirkungen waren geringfügig: ein Fall in der 200 mg Suprofengruppe, drei in der 650 mg Aspiringruppe und einer bei den Placebos. In Dosen von 200 und 400 mg erwies sich Suprofen als sicheres und wirksames, oral applizierbares Analgetikum zur Behandlung mittlerer bis schwerer Schmerzzustände nach Zahnbehandlungen, mit möglicherweise schnellerem Wirkungseintritt, verglichen mit 650 mg Aspirin oder 650 mg Aspirin plus Codein.

Efficacité analgésique orale du suprofen comparée à celle de l'aspirine, de l'aspirine plus codéine et du placébo chez les patients souffrant de douleurs dentaires postopératoires

Résumé. Le but de la présente étude a été d'évaluer l'efficacité analgésique et la sûreté de doses orales uniques de suprofen 200 et 400 mg en comparaison avec l'aspirine 650 mg plus codéine 60 mg, l'aspirine 650 mg et un placébo pour le soulagement de douleurs modérées à sévères consécutives à l'extraction de troisièmes molaires barrées. 157 patients ont terminé un essai par groupes parallèles, en double-aveugle, randomisé et stratifié, et ont été observés pendant au moins 4 h. Sur la base de chacune des mesures sommaires d'efficacité, SPID, % SPID, TOTPAR et évaluation globale, tous les quatre traitements actifs se sont montrés d'une efficacité plus ou moins égale et, du point de vue statistique, tous on été supérieurs au placébo. Par surcroît, le suprofen

logies s'est montré sensible que le placébo, à partir de après le début pour l'intens douleur, alors que les deux pirine ne sont pas apparus cébo avant 1 h. Les effets s minimes; 1 seul s'est déclar 200 mg, 3 avec l'aspirine e cébo. Il apparaît donc que 400 mg est un analgésique pour le soulagement de d postopératoires modérées à ble agir plus vite que l'aspi pirine 650 mg plus codéin

Efficacia del suprofen c orale rispetto ad aspirin codeina e placebo in pa dolore postoperatorio d

Sommario. Il presente s valutare l'efficacia analges dosi singole orali di supr rispetto ad aspirina 650 c aspirina 650 mg e placeb dolore, moderato o acut rimozione chirurgica del so. 157 pazienti hanno pa dio con selezione a caso, dose singola, stratificato e sono stati osservati per petto alle misurazioni di capi, lo SPID, lo SPID pe PAR, e in base a una va quattro trattamenti attivi approssimativamente di listicamente superiori al suprofen sia a 200 che a trato un'efficacia signif riore a quella del placebo

cébo. Par surcroît, le suprofen aux deux posologies s'est montré sensiblement plus efficace que le placébo, à partir d'une demi-heure après le début pour l'intensité moyenne de la douleur, alors que les deux traitements à l'aspirine ne sont pas apparus supérieurs au placébo avant 1 h. Les effets secondaires on été minimes; 1 seul s'est déclaré avec le suprofen 200 mg, 3 avec l'aspirine et et 1 avec le placébo. Il apparaît donc que le suprofen 200 et 400 mg est un analgésique oral sûr et efficace pour le soulagement de douleurs dentaires postopératoires modérées à sévères et il semble agir plus vite que l'aspirine 650 mg et l'aspirine 650 mg plus codéine 60 mg.

Efficacia del suprofen come analgesico orale rispetto ad aspirina, aspirina con codeina e placebo in pazienti sofferenti di dolore postoperatorio dentario

Sommario. Il presente studio si propone di valutare l'efficacia analgesica e la sicurezza di dosi singole orali di suprofen 200 e 400 mg rispetto ad aspirina 650 con codeina 60 mg, aspirina 650 mg e placebo nel controllo del dolore, moderato o acuto, conseguente alla rimozione chirurgica del terzo molare incluso. 157 pazienti hanno partecipato a uno studio con selezione a caso, in doppio cieco, a dose singola, stratificato e a gruppi paralleli, e sono stati osservati per almeno 4 ore. Rispetto alle misurazioni di efficacia per sommi capi, lo SPID, lo SPID percentuale e il TOTPAR, e in base a una valutazione globale, i quattro trattamenti attivi si sono dimostrati approssimativamente di pari efficacia, e statisticamente superiori al placebo. Inoltre, il suprofen sia a 200 che a 400 mg ha dimostrato un'efficacia significativamente superiore a quella del placebo rispetto all'intensità media del dolore a cominciare dall'osservazione dopo mezz'ora, mentre i due trattamenti a base di aspirina si sono dimostrati superiori al placebo solo all'osservazione dopo 1 ora. Gli effetti collaterali sono stati minimi: uno nel suprofen 200 mg, tre nell'aspirina 650 mg e uno nel placebo.

Eficacia analgésica oral del suprofen al compararlo con la aspirina, la aspirina con codeína y el placebo en pacientes con dolores dentales post-operatorios

Resumen. El propósito de este estudio fué evaluar la eficacia analgésica y la seguridad de una sóla dosis de suprofen de 200 y 400 mg al compararlo con 650 mg de aspirina con 60 mg de codeína, 650 mg de aspirina y el placebo en el alivio de dolores de moderados a fuertes resultantes de la excisión quirúrgica de cordales impactados. 157 pacientes terminaron un ensayo al azar, doble-ciego, de una sóla dosis, estratificado, de grupos paralelos y fueron observados por lo menos durante 4 horas. Basandose en cada una de las medidas de resumen de la eficacia, SPID, SPID por ciento, TOTPAR y una evaluación global, todos los cuatro tratamientos activos tuvieron una efectividad aproximadamente igual y todos fueron estadísticamente superiores al placebo. Además, el suprofen, en ambos niveles de dosificación fué significativamente más efectivo que el placebo, comenzando en la observación a la media hora, para el promedio de la intensidad del dolor, mientras que los dos tratamientos con la aspirina no fueron superiores al placebo hasta la observación a la hora. Los efectos adversos fueron mínimos; hubo uno con el suprofen de 200 mg, tres con la aspirina de 650 mg y uno con el placebo.

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Abraham Sunshine, MD, PC,
907 Fifth Avenue
New York, NY 10021 (USA)

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Comparison of Sup
Pain Secondary to

Y. Schuermans

St. Joseph Hospital, Merksplas.

Key Words. Suprofen · Ib

Abstract. 43 patients wit
suprofen 800 mg/day or ibı
improvement in subjective s
obtained with suprofen. Pa
improvement in pain on mc
investigators evaluated both
(over 75%) of cases. Both dr
ibuprofen group.

Introduction

Suprofen is a new, non-n
suitable for use in a variety
tions requiring alleviation of
studies have shown that supı
remarkably high separation
tivity from gastrointestinal i
vantage in a class of drugs w
associated with gastrointes
[1, 2]. The analgesic prope
are attributed to its inhibitic
tors which include inhibitic
din biosynthesis, interferer
glandin binding at sensory
and inhibition of bradykini